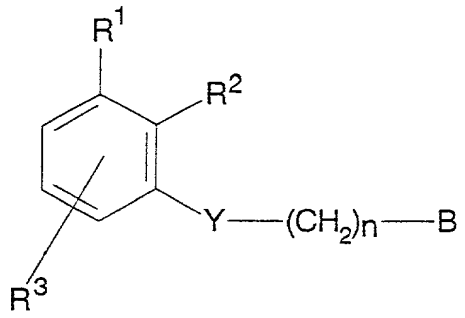
Claims

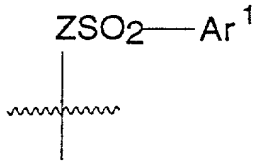
1. A compound of formula I,



I

wherein

one of R^1 and R^2 represents a structural fragment of formula Ia



Ia

and the other represents R^4;

Z represents O or $N(R^5)$;

R^3 represents one or more optional substituents selected from OH, halo, cyano, nitro, $C(O)OR^6$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

R^4 represents H, OH, halo, cyano, nitro, $C(O)OR^6$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

Ar^1 represents phenyl, C_{1-3} alkylphenyl, C_{1-3} alkyldiphenyl, C_{3-7} cycloalkyl, C_{1-3}-alkyl-C_{3-7}-cycloalkyl, C_{1-3}-alkyl-di-C_{3-7}-cycloalkyl, naphthyl, C_{1-3} alkylnaphthyl, thienyl, imidazolyl or isoxazolyl, all of which may be substituted by one or more substituent selected from OH, halo, cyano, nitro, $C(O)OR^6$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally

substituted and/or terminated by one or more halo or hydroxy group) or $N(R^7)R^8$;

R^5 represents H, C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl (which three latter groups are optionally substituted and/or terminated by one or more substituent selected from OH, halo, cyano, nitro, $C(O)OR^9$, $C(O)N(R^{10})R^{11}$, $P(O)(R^{12})R^{13}$, $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$, $S(O)_2N(R^{18})R^{19}$, C_{1-6} alkoxy or C_{1-6} alkyl (which two latter groups are optionally substituted and/or terminated by one or more halo or hydroxy group) or $N(R^{20})R^{21}$);

Y represents O, S, S(O), $S(O)_2$ or $N(R^{22})$;

R^{10} and R^{11} independently represent H, OR^{23}, $C(O)R^{24}$, $OC(O)R^{25}$, $C(O)OR^{26}$, C_{1-4} alkyl, (which latter group is optionally substituted and/or terminated by one or more substituent selected from C_{1-4} alkyl, OR^{27}, $N(R^{28})R^{29}$, $C(O)OR^{30}$ $C(O)N(R^{31})R^{32}$, $P(O)(R^{33})R^{34}$, $P(O)(OR^{35})OR^{36}$ and $S(O)_2N(R^{37})R^{38}$), $-(CH_2CH_2O-)_pR^{39}$ or, together with the nitrogen atom to which they are attached, form a C_{4-7} nitrogen-containing, aromatic or non-aromatic, ring which ring may contain a further heteroatom or group (as appropriate) selected from O, S and $N(R^{40})$ and may further be substituted by one or more substituent selected from $C(O)R^{41}$, $C(O)OR^{42}$ or $C(O)N(R^{43})R^{44}$;

R^{28}, R^{29}, R^{30}, R^{31}, R^{32} and R^{40} independently represent H or C_{1-6} alkyl, which latter group is optionally substituted and/or terminated by one or more substituent selected from $C(O)R^{45}$, $C(O)OR^{46}$ or $C(O)N(R^{47})R^{48}$;

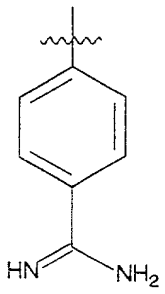
at each occurance, R^6, R^7 and R^8 independently represent H or C_{1-4} alkyl;

R^9, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47} and R^{48} independently represent H or C_{1-4} alkyl;

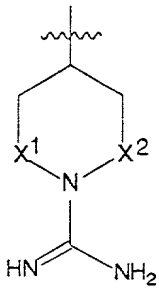
n represents 0, 1, 2, 3 or 4;

p represents 1, 2, 3, 4, 5 or 6; and

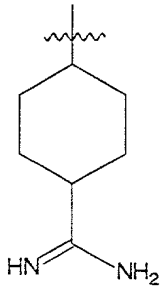
B represents a structural fragment of formula Ib, Ic, Id or Ie



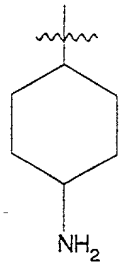
Ib



Ic



Id



Ie

wherein

X^1 and X^2 independently represent a single bond or CH_2;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein, when B represents a structural fragment of formula Ib, Id, Ie or Ic in which latter fragment X^1 and X^2 both represent CH_2, then n represents 2.

3. A compound of formula I, as defined in one Claim 1, wherein n represents 2.

4. A compound of formula I, as defined in any one of the preceding claims, wherein R^2 represents a structural fragment of formula Ia and R^1 represents R^4.

5. A compound of formula I, as defined in any one of the preceding claims, wherein Z represents O or $N(R^5)$, in which latter case R^5 represents C_{1-6} alkyl terminated by $C(O)N(R^{10})R^{11}$.

6. A compound of formula I, as defined in any one of the preceding claims, wherein R^3 is not present, or represents methyl, chloro or methoxy.

7. A compound of formula I, as defined in any one of the preceding claims, wherein Ar^1 represents substituted phenyl.

8. A compound of formula I, as defined in any one of the preceding claims wherein Y represents O.

9. A compound of formula I, as defined in any one of the preceding claims wherein B represents a structural fragment of formula Ib.

10. A compound as claimed in Claim 1 which is:
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}benzenesulfonamide;
benzenesulfonic acid-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methyl}phenyl ester;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-chlorobenzenesulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-cyanobenzene-sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-fluorobenzene-sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2-(trifluoromethoxy)-benzenesulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-4-fluorobenzene-sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dimethylbenzene-sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-5-chlorothiophene-2-sulfonamide;
N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-1-methylimidazole-3-sulfonamide;
N-{3-[2-(4-aminoiminomethylp henyl)ethoxy]phenyl}-3,5-dimethylisoxazole-

4-sulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}benzylsulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-2,5-dichlorothiophene-3-sulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl}-2-chlorobenzenesulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-2-methylphenyl}-benzenesulfonamide;

N-{5-[2-(4-aminoiminomethylphenyl)ethoxy]-2-methylphenyl}benzene-sulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl}benzene-sulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}benzenesulfonamide;

N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid, ethyl ester;

N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetamide;

N-(2-chlorophenyl)sulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylaminoacetic acid;

N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, ethyl ester;

2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino}propanamide;

N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid;

N-(2-chlorophenyl)sulfonyl-2-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}propanoic acid, methyl ester;

N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid, ethyl ester;

3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-

methylphenylamino}butanamide;

N-(2-chlorophenyl)sulfonyl-3-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}butanoic acid;

N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid, ethyl ester;

4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-N-(2-chlorophenyl)sulfonyl-5-methylphenylamino}pentanamide;

N-(2-chlorophenyl)sulfonyl-4-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}pentanoic acid;

N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid, ethyl ester;

5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]- N-(2-chlorophenyl)sulfonyl-5-methylphenylamino}pentanamide;

N-(2-chlorophenyl)sulfonyl-5-{3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenylamino}hexanoic acid;

N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylamino-acetic acid, ethyl ester;

N-phenylsulfonyl-3-[2-(4-aminoiminomethylphenyl)ethoxy]phenylamino-acetic acid;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(2-hydroxyethyl)-benzenesulfonamide;

N-{3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl}-N-(dimethyloxo-phosphinylmethyl)-benzenesulfonamide;

2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methylphenyl ester;

benzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]phenyl ester;

2-chloro-4-fluorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)-ethoxy]-5-chlorophenyl ester;

2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-methoxyphenyl ester;

2-chlorobenzenesulfonic acid, 3-[2-(4-aminoiminomethylphenyl)ethoxy]-5-ethylphenyl ester;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,4,5-trichloro-benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-5-methoxybenzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dibromo-benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,5-dichloro-benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)-ethylthio]-phenyl}-2-methoxy-5-methylbenzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2,3,5,6-tetramethylbenzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dimethoxy-benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3-bromo-benzenesulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-3,4-dibromobenzene-sulfonamide;

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-2-chloro-4-fluorobenzenesulfonamide; or

N-{2-[2-(4-aminoiminomethylphenyl)ethylthio]phenyl}-5-bromo-2-methoxybenzenesulfonamide.

11. A compound of formula I, as defined in Claim 1, provided that R^1 represents a structural fragment of formula Ia and R^2 represents R^4.

12. A compound of formula I, as defined in Claim 1, provided that Ar^1

represents optionally substituted phenyl.

13. A compound of formula I, as defined in Claim 1, provided that R^5 is not substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$.

14. A compound of formula I, as defined in Claim 1, provided that R^{10} and/or R^{11} represent H or unsubstituted C_{1-4} alkyl.

15. A compound of formula I, as defined in Claim 1, provided that Y represents O, S or $N(R^5)$.

16. A compound of formula I, as defined in Claim 1, provided that B represents a structural fragment of formula Ib, Ic or Id.

17. A compound of formula I, as defined in Claim 1, provided that R^2 represents a structural fragment of formula Ia and R^1 represents R^4.

18. A compound of formula I, as defined in Claim 1, provided that Ar^1 does not represent optionally substituted phenyl.

19. A compound of formula I, as defined in Claim 1, provided that R^5 is substituted by $P(O)(OR^{14})OR^{15}$, $S(O)_2(R^{16})R^{17}$ or $S(O)_2N(R^{18})R^{19}$.

20. A compound of formula I, as defined in Claim 1, provided that R^{10} and/or R^{11} do not represent H or unsubstituted C_{1-4} alkyl.

21. A compound of formula I, as defined in Claim 1, provided that Y represents S(O) or $S(O)_2$.

22. A compound of formula I, as defined in Claim 1, provided that B

represents a structural fragment of formula Ie.

23. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

24. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

25. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

26. A compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

27. A compound of formula I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

28. The use of a compound I as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

29. The use as claimed in Claim 28, wherein the condition is thrombosis.

30. The use of a compound defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

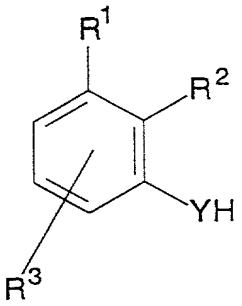
31. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 22, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

32. A method as claimed in Claim 31, wherein the condition is thrombosis.

33. A method as claimed in Claim 31, wherein the condition is hypercoagulability in blood and tissues.

34. A process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,



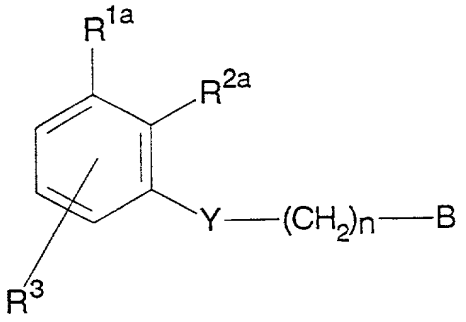
II

wherein R^1, R^2, R^3 and Y are as defined in Claim 1 with a compound of formula III,

$$L^1\text{-}(CH_2)_n\text{-}B \qquad \text{III}$$

wherein L^1 represents a suitable leaving group and n and B are as defined in Claim 1;

(b) reaction of a compound of formula IV,



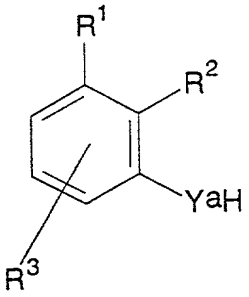
IV

wherein one of R^{1a} and R^{2a} represents ZH and the other represents R^4, and Z, R^3, R^4, Y, n and B are as defined in Claim 1 with a compound of formula V,

$$L^2\text{-}SO_2\text{-}Ar^1 \qquad V$$

wherein L^2 is a suitable leaving group and Ar^1 is as defined in Claim 1;

(c) for compounds of formula I in which Y represents O or S, reaction of a compound of formula VI,



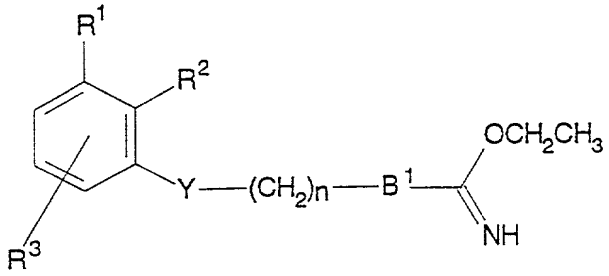
VI

wherein Y^a represents O or S and R^1, R^2 and R^3 are as defined in Claim 1 with a compound of formula VII,

$$HO\text{-}(CH_2)_n\text{-}B \qquad VII$$

wherein n and B are as defined in Claim 1;

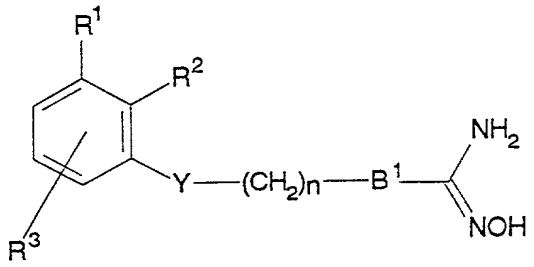
(d) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula VIII,



VIII

wherein B^1 represents 1,4-phenylene or 1,4-cyclohexylene and R^1, R^2, R^3, Y and n are as defined in Claim 1 with ammonia gas;

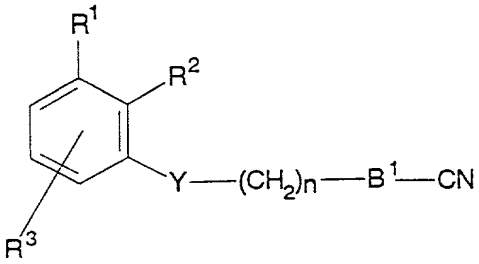
(e) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reduction of a compound of formula IX,



IX

wherein R^1, R^2, R^3, Y and n are as defined in Claim 1 and B^1 is as defined above;

(f) for compounds of formula I wherein B represents a structural fragment of formula Ib or Id, reaction of a compound of formula X,



X

wherein R^1, R^2, R^3, Y and n are as defined in Claim 1 and B^1 is as defined above;

(g) for compounds of formula I wherein Y represents S(O) or $S(O)_2$, oxidation of a corresponding compound of formula I wherein Y represents S;

(h) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, reaction of a corresponding compound of formula I wherein Z represents NH with a compound of formula XI,

$$L^2\text{-}R^{5a} \qquad \text{XI}$$

wherein R^{5a} represents optionally substituted C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl and L^2 is as defined above;

(i) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)N(R^{10})R^{11}$, reaction of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated, by $C(O)OR^9$, and R^9 is as defined in Claim 1, with a compound of formula XII,

$$HN(R^{10})R^{11} \qquad \text{XII}$$

wherein R^{10} and R^{11} are as defined in Claim 1;

(j) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by C(O)OH, hydrolysis of a corresponding compound of formula I wherein R^5 represents C_{1-6} alkyl, phenyl or C_{1-3} alkylphenyl, all of which are substituted and/or terminated by $C(O)OR^9$ and R^9 represents C_{1-4} alkyl; or

(k) for compounds of formula I wherein Z represents $N(R^5)$ and R^5 represents $(CH_2)_2C(O)OR^9$ and R^9 is as defined in Claim 1, reaction of a corresponding compound of formula I wherein R^5 represents H with a compound of formula XIII,

CH_2=CH-C(O)OR^9 XIII

wherein R^9 is as defined in Claim 1.